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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,474	04/20/2004	Tianmin Zhu	AM101007	7099

28940 7590 06/24/2010

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EXAMINER	
PACKARD, BENJAMIN J	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
06/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/828,474	ZHU ET AL.	
	Examiner	Art Unit	
	Benjamin Packard	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,14-20,32-38,50-56,68-80 and 92-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,35,50,53,56,68,69,71,74,77,80 and 93-95* is/are rejected.

7)☒ Claim(s) *15,16,18,19,33,34,36,37,39,51,52,54,55,70,72,73,75,76,78,79,92 and 96* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

The indicated allowability of claims 1, 2, 14-20, 32-38, 50-56, 68-80, and 92-96 is withdrawn in view of the newly discovered reference(s) to Wandless et al (US Pregrant Pub 2003/0194749). Rejections based on the newly cited reference(s) follow.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 14, 20, 32, and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Wandless et al (US Pregrant Pub 2003/0194749).

Wandless et al teaches a control compound prepared where wortmannin moiety was linked via a PEG linker to a methyl group (¶ 353). The modification is taught to have been made at the C11 hydroxy group (¶ 352). The size of the linker is taught to be from 150-1500 amu (¶ 181) which appears to be within the instantly claimed broadest range, but does not anticipate the specific ranges of the dependant claims..

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 17, 35, 50, 53, 56, and 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wandless et al (US Pregrant Pub 2003/0194749) in view of Greenwald et al (Journal of Controlled Release 74 (2001) 159-171, see IDS dated 4/20/04).

Wandless et al is discussed above and further teaches the active site for PI 3-kinase action is disclosed to be the electrophilic C21 position of wortmannin (¶ 117 and Fig 2).

Wandless et al does not teach an embodiment with a PEG group within the narrower scope of ranges instantly claimed or modification of the C17 hydroxy group.

Greenwald et al teaches ester carbonyl bonds were formed to paclitaxel, a small molecule organic drug, using PEG with molecular weights from 6,000-50,000, thereby forming a highly water soluble ester of paclitaxel which functioned as a prodrug (pg 160 section 3.1 and pg 161 section 3.2). The most dramatic change occurred at a molecular weight of 30,000 (*id.*). Specifically, the $t_{1/2}$ for renal clearance decreased with an increase in molecular weight. Additionally, high molecular weight PEGs were used to modify the distribution, metabolism, and excretion of paclitaxel and camptothecin (*id.*).

Greenwald et al does not teach the modification of Wortmannin.

It would have been obvious to one of ordinary skill in the art, when making the compounds of Wandless et al to use PEGs which are known to be effective for producing prodrugs of cancer agents, such as the range of PEGs disclosed in Greenwald. Additionally, it would have been obvious to optionally attach the PEG linker to the C17 hydroxy group where the active site is not at the C17 carbon.

Applicants previously asserted that no pegulated small molecule organic drug previously showed in vivo activity as a factor of unpredictability in the art.

Examiner now disagrees. Greenwald et al teaches the prodrug forms of paclitaxel, where the breakdown occurred in a predictable fashion (Greenwald, pg 160, section 3.1). Further, Greenwald et al teaches by varying the size of the PEG, the circulation lifetime of the water soluble modified drug is extended relative to the rate of hydrolysis, resulting in a gradual controlled release of the drug (Greenwald, pg 161 last ¶).

Claims 68, 69, 71, 74, 77, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wandless et al (US Pregrant Pub 2003/0194749) in view of Greenwald et al (Advanced Drug Delivery Reviews 55 (2003) 217–250, see IDS dated 4/20/04), the combination further in view of Patani et al (Chemical Reviews Vol 96 No 8 (1996) pp 3147-3176).

The teachings of Wandless et al and Greenwald et al are discussed above but do not teach using a PEGSH in place of the ester linked PEG.

Patani et al teaches oxygen and sulfur are bioisosteres when attached via two single bonds and commonly substituted while still retaining corresponding activity (pg 3155-3156 section B2).

Patani et al does not teach modifying pegulated Wortmannin.

It would have been obvious to one of ordinary skill in the art to substitute sulfur for oxygen in the compounds both disclosed and made obvious by Wandless et al and Greenwald et al, given the atoms are bioisostere of each other and are commonly substituted in drug design.

Claims 17, 35, 50, 53, 56, and 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creemer et al (US 5,480,906, see IDS dated 4/20/04) in view of Greenwald et al (Journal of Controlled Release 74 (2001) 159-171, see IDS dated 4/20/04).

Creemer et al is teaches Wortmannin compounds which may be modified at the C11 and C17 positions, while still retaining PI-3 kinase inhibition effect (claim 1).

Creemer et al does not teach pegulating the Wormannin.

Greenwald et al teaches ester carbonyl bonds were formed to paclitaxel, a small molecule organic drug, using PEG with molecular weights from 6,000-50,000, thereby forming a highly water soluble ester of paclitaxel which functioned as a prodrug (pg 160 section 3.1 and pg 161 section 3.2). The most dramatic change occurred at a molecular weight of 30,000 (*id.*). Specifically, the $t_{1/2}$ for renal clearance decreased with an increase in molecular weight. Additionally, high molecular weight PEGs were used to modify the distribution, metabolism, and excretion of paclitaxel and camptothecin (*id.*).

Greenwald et al does not teach the modification of Wortmannin.

It would have been obvious to one of ordinary skill in the art, when making the compounds of Wandless et al to use PEGs which are known to be effective for producing prodrugs of cancer agents, such as the range of PEGs disclosed in Greenwald. Additionally, it would have been obvious to optionally attach the PEG linker to the C17 hydroxy group where the active site is not at the C17 carbon.

Applicants previously asserted that no pegulated small molecule organic drug previously showed in vivo activity as a factor of unpredictability in the art.

Examiner now disagrees. Greenwald et al teaches the prodrug forms of paclitaxel, where the breakdown occurred in a predictable fashion (Greenwald, pg 160, section 3.1). Further, Greenwald et al teaches by varying the size of the PEG, the circulation lifetime of the water soluble modified drug is extended relative to the rate of hydrolysis, resulting in a gradual controlled release of the drug (Greenwald, pg 161 last ¶). Additionally, Examiner notes the prior art teaches in vivo efficacy for a wide range of

molecular weight pegs, and the instant generic claims appear to include the higher range of molecular weights disclosed.

Claims 68, 69, 71, 74, 77, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creemer et al (US 5,480,906, see IDS dated 4/20/04) in view of Greenwald et al (Advanced Drug Delivery Reviews 55 (2003) 217–250), the combination further in view of Patani et al (Chemical Reviews Vol 96 No 8 (1996) pp 3147-3176).

The teachings of Creemer et al and Greenwald et al are discussed above but do not teach using a PEGSH in place of the ester linked PEG.

Patani et al teaches oxygen and sulfur are bioisosteres when attached via two single bonds and commonly substituted while still retaining corresponding activity (pg 3155-3156 section B2).

Patani et al does not teach modifying pegulated Wortmannin.

It would have been obvious to one of ordinary skill in the art to substitute sulfur for oxygen in the compounds both disclosed and made obvious by Wandless et al and Greenwald et al, given the atoms are bioisostere of each other and are commonly substituted in drug design.

Allowable Subject Matter

Claims 15-16, 18-19, 33-34, 36-37, 51, 52, 54, 55, 39, 70, 72, 73, 75, 76, 78, 79, 92, and 96 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

These claims are directed to forming pegulated forms of wortmannin, which according Greenwald et al would not be expected to have in vivo efficacy, where at pg 161 section 3.1 it is disclosed that while in vitro efficacy is shown, no in vivo activity is produced. This was replicated when tested using paclitaxel ester PEG-5000 On the other hand, the independent claims and the dependant claims rejected in the obviousness rejections above include higher molecular weight PEGs which are disclosed to have in vivo efficacy and therefore are properly rejected as obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-R 8-6 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin Packard/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612